TENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
ROYAUME-UNI

Date of mailing (day/month/year)
04 December 2000 (04.12.00)

Applicant's or agent's file reference
HMJ02835WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/04206

International filing date (day/month/year)
13 December 1999 (13.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
BIOCOMPATIBLES LIMITED
Frensham House
Farnham Business Park
Weydon Lane
Farnham
Surrey GU9 8QL
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
BIOCOMPATIBLES LIMITED
Chapman House
Farnham Business Park
Weydon Lane
Farnham
Surrey GU9 8QL
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
R. Chrem
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 August 2000 (07.08.00)	
International application No. PCT/GB99/04206	**Applicant's or agent's file reference** HMJ02835WO
International filing date (day/month/year) 13 December 1999 (13.12.99)	**Priority date** (day/month/year) 11 December 1998 (11.12.98)
Applicant MUIR, Andrew, Victor, Graham et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 June 2000 (23.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
ROYAUME-UNI

Date of mailing (day/month/year) 21 February 2000 (21.02.00)	
Applicant's or agent's file reference HMJ02835WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/04206	International filing date (day/month/year) 13 December 1999 (13.12.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 11 December 1998 (11.12.98)
Applicant BIOCOMPATIBLES LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
11 Dece 1998 (11.12.98)	98310163.5	EP	25 Janu 2000 (25.01.00)

The International Bureau of WIPO
34, chemin des Col mbettes
1211 G neva 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer

R. Chrem

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
GRANDE BRETAGNE

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.09.2000
Applicant's or agent's file reference HMJ02835WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04206	13/12/1999	11/12/1998

Applicant
BIOCOMPATIBLES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Le Bolloch, C Tel.+49 89 2399-8091

Form PCT/IPEA/416 (July 1992)

ENT COOPERATION TRE[redacted]Y

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMJ02835WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04206	13/12/1999	11/12/1998
International Patent Classification (IPC) or national classification and IPC C08F246/00		
Applicant BIOCOMPATIBLES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/06/2000	08.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Knutzen-Mies, K Telephone No. +49 89 2399 8525

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04206

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-29 as originally filed

Claims, No.:

1-31 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-31
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

ad section V.:

None of the documents cited in the international search report, which have also been acknowledged at pages 1 and 2 of the present description, discloses or fairly suggests a crosslinked polymer obtainable by radical polymerisation of unsaturated monomers comprising a zwitterionic monomer, an aromatic group containing monomer and a crosslinking monomer as defined in claim 1 of the present application.

In particular, the combination of specific zwitterionic monomers with an aromatic group containing monomer to provide a polymer suitable for optical purposes such as eg intra ocular lenses, ie requiring a high refractive index, is not taught or suggested by the prior art.

The subject matter of claims 1 - 31 of the present application is therefore considered to fulfil the requirements of Article 33(2) - (4) PCT.

ad section VIII.:

The preferred embodiment of claim 5, ie R^9 being an ethylene or an oligo(ethylene-oxy)ethylene group, and the preferred range of crosslinking monomer in claim 10, ie 0.5 to 3 % by weight, have no descriptive counterpart (Article 84 PCT).

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C08F 246/00, G02B 1/04

A1

(11) International Publication Number: WO 00/35980

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/GB99/04206

(22) International Filing Date: 13 December 1999 (13.12.99)

(30) Priority Data:
98310163.5 11 December 1998 (11.12.98) EP

(71) Applicant *(for all designated States except US)*: BIOCOMPATIBLES LIMITED [GB/GB]; Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MUIR, Andrew, Victor, Graham [GB/GB]; 5 Rupert Road, Guildford, Surrey GU2 5NE (GB). ROWAN, Lee [GB/GB]; 11 Wakehurst Close, Maple Park, Nuneaton, Warwickshire CV11 4YF (GB). JONES, Stephen, Alister [GB/GB]; Biocompatibles Limited, Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB). STEDMAN, John, Charles [GB/GB]; Biocompatibles Limited, Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: CROSSLINKED POLYMERS AND REFRACTIVE DEVICES FORMED THEREFROM

(57) Abstract

A polymer is formed of ethylenically unsaturated monomers including a zwitterionic monomer, an aromatic monomer and a cross–linking monomer. Preferably the crosslinking monomer includes at least one aromatic group containing compound and at least one aliphatic group containing compound. The polymer is water–swellable and a hydrogel has optical and mechanical properties rendering it suitable for use as an intraocular refractive device such as an intraocular lens.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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CROSSLINKED POLYMERS AND REFRACTIVE DEVICES FORMED THEREFROM

Background of the Invention

The present invention relates to a polymeric composition, which is a crosslinked water swellable polymer, the hydrogel of which is transparent and has a high refractive index, rendering it useful for use in a refractive device, for instance an intraocular lens.

Relevant Prior Art

Various products have been developed for replacing or augmenting the natural lens. Replacement lenses may be used where the original lens is clouded by cataracts. Lenses which augment the natural lens and which are intended to be inserted into the eye, include intraocular contact lenses, corneal implants, corneal inlays and corneal onlays.

A method of implanting an intraocular lens in a rolled up form, to minimise the size of the incision is in widespread use. Such a device is described in US-A-4,573,998 and US-A-4,702,244. In these specifications, the material of the lens is described as having a shape memory. The device thus recovers its original conformation after being released from the restraining insertion device through which it is introduced. The above specifications do not describe in any detail the materials used to form the lens.

In US-A-4,608,049, a foldable intraocular lens is formed of a silicone rubber or a crosslinked hydroxyethylmethacrylate: N-vinyl-2-pyrrolidone: methacrylic acid polymer, that is a water-swellable material.

Further descriptions of hydrogel intraocular lenses are by Barrett in US-A-4,664,666. Barrett uses a hydrogel of hydroxyethylmethacrylate, a common component of hydrogel contact lens compositions. One problem with poly HEMA hydrogels is that the refractive index of the gel is relatively low. It is preferred for a hydrogel to have higher refractive indices, for instance at least 1.45, up to around 1.60.

Higher refractive index materials are described in EP-A-0485197. The polymers must be formed of at least two aryl acrylate polymers, for instance 2-phenylethyl acrylate and 2-phenylethyl methacrylate. The crosslinker is selected from aliphatic diacrylates. The refractive indices of the material is in the range 1.553 to 1.556. The polymers are not, however, hydrogels (that is they are not water-swellable).

EP-A-0308130 describes elastic intraocular lenses formed of copolymers of methacrylate and acrylate esters which are respectively relatively hard and relatively soft at body temperature. The monomers are all aliphatic acrylates. The crosslinker is an aliphatic dimethacrylate.

In our earlier application WO-A-9207885, we describe crosslinked polymers formed of zwitterionic monomer and nonionic copolymerisable monomer, and hydrogel lenses formed therefrom. The examples all used an alkyl acrylate or hydroxyalkylacrylate comonomer. The crosslinking monomers were all aliphatic di-ethylenically unsaturated compounds.

In EP-A-0563299 a copolymer of a zwitterionic monomer and a nonionic monomer is used as a contact lens. In the worked examples, comonomers are hydroxyethylmethacrylate, N-vinylpyrollidone and methylmethacrylate. Crosslinkers are all aliphatic compounds (allyl methacrylate and diethylene glycol di-methacrylate).

In US-A-5,391,669 and US-A-5,270,415, hydrogels formed of balanced charge ion pairs and nonionic comonomer are used as contact lenses. The balanced charge ion pair may be a zwitterionic monomer. In the worked examples, the nonionic comonomers are selected from hydroxyethyl methacrylate, silyl group containing monomers, alkyl methacrylates, hydroxypropyl methacrylate, fluoroalkyl methacrylate and hydroxypropyl methacrylamide. Crosslinkers used in the worked examples are all aliphatic compounds.

Summary of the Invention

A new crosslinked polymer according to the invention is obtainable by radical polymerisation of ethylenically unsaturated monomers including

a) a zwitterionic monomer of the general formula I

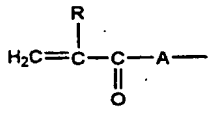
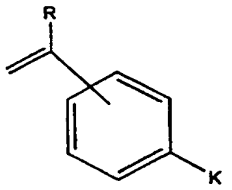
YBX I

wherein

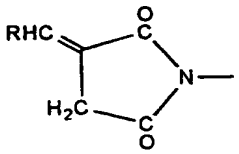
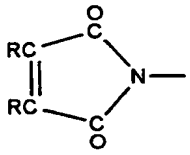
B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X or Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group; and

Y is an ethylenically unsaturated polymerisable group selected from

CH_2=C(R)-CH_2-O-, CH_2=C(R)-CH_2OC(O)-, CH_2=C(R)OC(O)-, CH_2=C(R)-O-, CH_2=C(R)CH_2OC(O)N(R^1)-, R^2OOCCR=CRC(O)-O-, RCH=CHC(O)O-, RCH=C(COOR^2)CH_2-C(O)-O-,


and


wherein:

R is hydrogen or a C_1-C_4 alkyl group;

R^1 is hydrogen or a C_1-C_4 alkyl group or R^1 is -B-X where B and X are as defined above; and

R^2 is hydrogen or a C_{1-4} alkyl group or BX where B and X are as defined above;

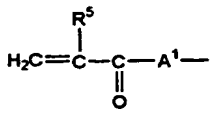
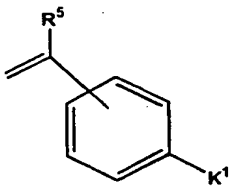
A is -O- or -NR^1-;

K is a group -$(CH_2)_pOC(O)$-, -$(CH_2)_pC(O)O$-, - $(CH_2)_pOC(O)O$-, -$(CH_2)_pNR^3$-, -$(CH_2)_pNR^3C(O)$-, -$(CH_2)_pC(O)NR^3$-, -$(CH_2)_pNR^3C(O)O$-, -$(CH_2)_pOC(O)NR^3$-, -$(CH_2)_pNR^3C(O)NR^3$- (in which the groups R^3 are the same or different), -$(CH_2)_pO$-, -$(CH_2)_pSO_3$ -, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R^3 is hydrogen or a C_1-C_4 alkyl group.

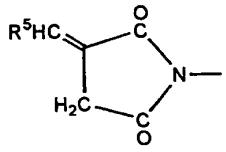
b) an aromatic group containing monomer of the general formula II

Y^1R^4 II

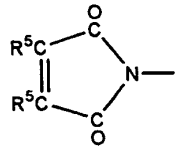
wherein Y^1 is selected from

$CH_2=C(R^5)-CH_2-O-$, $CH_2=C(R^5)-CH_2\ OC(O)-$, $CH_2=C(R^5)OC(O)-$, $CH_2=C(R^5)-O-$, $CH_2=C(R^5)CH_2OC(O)N(R^6)-$, $R^7OOCCR^5=CR^5C(O)-O-$, $R^5CH=CHC(O)O-$, $R^5CH=C(COOR^7)CH_2-C(O)-O-$,



and



wherein:

R^5 is hydrogen or a C_1-C_4 alkyl group;

R^6 is hydrogen or a C_1-C_4 alkyl group or R^5 is R^3;

R^7 is hydrogen or a C_{1-4} alkyl group or R^3;

A^1 is -O- or $-NR^5-$; and

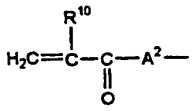
K^1 is a group $-(CH_2)_qOC(O)-$, $-(CH_2)_qC(O)O-$, $-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^8-$, $-(CH_2)_qNR^8C(O)-$, $-(CH_2)_qC(O)NR^8-$, $-(CH_2)_qNR^8C(O)O-$, $-(CH_2)_qOC(O)NR^8-$, $-(CH_2)_qNR^8C(O)NR^8-$ (in which the groups R^8 are the same or different), $-(CH_2)_qO-$, $-(CH_2)_qSO_3-$, or a valence bond and p is from 1 to 12 and R^8 is hydrogen or a C_1-C_4 alkyl group;

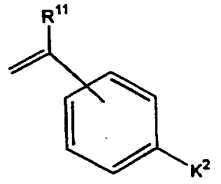
and R^4 is an aromatic group; and

c) a cross-linking monomer of the general formula III

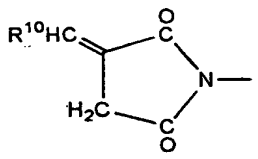
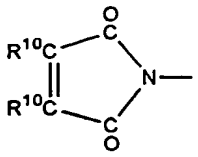
$$(Y^2)_nR^9 \qquad \text{III}$$

in which n is an integer of at least 2, each Y^2 is selected from





$CH_2=C(R^{10})-CH_2-O-$, $CH_2=C(R^{10})-CH_2\ OC(O)-$, $CH_2=C(R^{10})OC(O)-$, $CH_2=C(R^{10})-O-$, $CH_2=C(R^{10})CH_2OC(O)N(R^{11})-$, $R^{12}OOCCR^{10}=CR^{10}C(O)-O-$, $R^{10}CH=CHC(O)O-$, $R^{10}CH=C(COOR^{12})CH_2-C(O)-O-$,


and


wherein:

R^{10} is hydrogen or a C_1-C_4 alkyl group;

R^{11} is hydrogen or a C_1-C_4 alkyl group or R^{11} is R^3;

R^{12} is hydrogen or a C_{1-4} alkyl group or R^3;

A^2 is -O- or -NR^{11}-;

K^2 is a group -$(CH_2)_rOC(O)$-, -$(CH_2)_rC(O)O$-, - $(CH_2)_rOC(O)O$-, -$(CH_2)_rNR^{12}$-, -$(CH_2)_rNR^{13}C(O)$-, -$(CH_2)_rC(O)NR^{13}$-, -$(CH_2)_rNR^{13}C(O)O$-, -$(CH_2)_rOC(O)NR^{13}$-, -$(CH_2)_rNR^{13}C(O)NR^{13}$- (in which the groups R^{13} are the same or different), -$(CH_2)_rO$-, -$(CH_2)_rSO_3$ - or a valence bond and r is from 1 to 12 and R^{13} is hydrogen or a C_1-C_4 alkyl group;

and R^9 is an n-functional organic group.

Suitable examples of aromatic groups R^4 are optionally substituted aralkyl and alkaryl groups. Most preferably, a group R^4 is an unsubstituted aryl or aralkyl group, in which the alkyl group has 1 to 4 carbon atoms, for instance benzyl, 2-phenylethyl or phenyl.

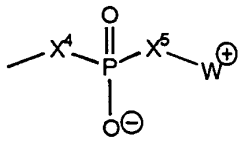
For optimum copolymerisability, the groups Y, Y^1 and Y^2 have the same general definition. Most preferably each such group is an (alk) acrylic or a styrenic group. An acrylic group, H_2C=C(H or Me)CO-(O or NH) are particularly preferred. Preferably all such groups are either methacrylic R = R^5 = R^{10} = Me) or acrylic (R, R^5, R^{10} = hydrogen), and are preferably all ester or amide derivatives thereof. Most conveniently, the monomers are all acrylic esters, generally either methacrylate esters or acrylate esters.

In the invention, it is found that optimum crosslinking of the aromatic and zwitterionic monomers is achieved where a crosslinking monomer of the formula III in which the group R^9 is an aromatic group is included. Suitable aromatic groups are, for instance, phenylene, alkarylene, aralkylene, and bisphenol A-type groups. Most preferably the crosslinker includes bisphenol A dimethacrylate. The crosslinker may be di-, tri-, tetra- or higher functional, for instance an oligomeric or polymeric compound.

It is found to be particularly preferred for the crosslinking monomer to include a monomer of the general formula III in which the group R^9 is an aliphatic group. Suitable aliphatic groups R^9 are C_{2-8}-alkylene, C_{2-4}-alkyleneoxy - C_{2-4}-alkylene or oligo(C_{2-4}-alkyleneoxy) - C_{2-4}-alkylene (e.g. $-(CH_2CH_2O)_tCH_2CH_2-$, where t is 1-50).

Most preferably a mixture of crosslinking agents is included, including at least one crosslinking agent in which R^9 is an aromatic group and at least one crosslinking agent in which R^9 is an aliphatic group.

In the general formula I, the zwitterionic group preferably has the general formula IV



IV

in which the moieties X^4 and X^5, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C_{1-12}-alkylene group,

preferably in which W^+ is a group of formula

$-W^1-N^+R^{14}_3$, $-W^1-P^+R^{15}_3$, $-W^1-S^+R^{15}_2$ or $-W^1$-Het$^+$ in which:

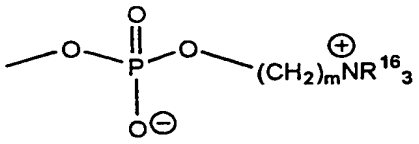
W^1 is alkylene of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl, alkylene aryl, aryl alkylene, or alkylene aryl alkylene, disubstituted cycloalkyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R^{14} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl or two of the groups R^{14} together with the nitrogen atom to which they are attached form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{14} together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^{14} is substituted by a hydrophilic functional group, and

the groups R^{15} are the same or different and each is R^{14} or a group OR^{14}, where R^{14} is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

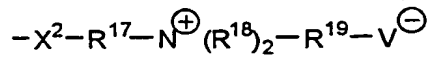
Most preferably, the zwitterionic group of the formula IV, has the general formula V:



V

where the groups R^{16} are the same or different and each is hydrogen or C_{1-4} alkyl, and m is from 1 to 4, in which preferably the groups R^{16} are the same.

Alternatively, the zwitterionic group may be a betaine group (ie in which the cation is closer to the backbone), for instance a sulpho-, carboxy- or phospho-betaine. A betaine group should have no overall charge and is preferably therefore a carboxy- or sulpho-betaine. If it is a phosphobetaine the phosphate terminal group must be a diester, i.e., be esterified with an alcohol. Such groups may be represented by the general formula VI



VI

in which X^2 is a valence bond, -O-, -S- or -NH-, preferably -O-;

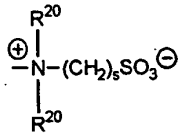
V is a carboxylate, sulphonate or phosphate diester(monovalently charged) anion;

R^{17} is a valence bond (together with X^2) or alkylene -C(O)alkylene- or -C(O)NHalkylene preferably alkylene and preferably containing from 1 to 6 carbon atoms in the alkylene chain;

the groups R^{18} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms or the groups R^{18} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 atoms; and

R^{19} is alkylene of 1 to 20, preferably 1 to 10, more preferably 1 to 6 carbon atoms.

One preferred sulphobetaine monomer has the formula VII



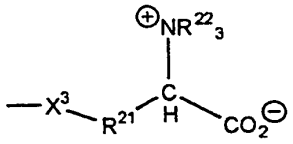
VII

where the groups R^{20} are the same or different and each is hydrogen or C_{1-4} alkyl and s is from 2 to 4.

Preferably the groups R^{20} are the same. It is also preferable that at least one of the groups R^{20} is methyl, and more preferable that the groups R^{20} are both methyl.

Preferably s is 2 or 3, more preferably 3.

Alternatively the zwitterionic group may be an amino acid moiety in which the alpha carbon atom (to which an amine group and the carboxylic acid group are attached) is joined through a linker group to the backbone of polymer A. Such groups may be represented by the general formula VIII



VIII

in which X^3 is a valence bond, -O-, -S- or -NH-, preferably -O-,

R^{21} is a valence bond (optionally together with X^3) or alkylene, -C(O)alkylene- or -C(O)NHalkylene, preferably alkylene and preferably containing from 1 to 6 carbon atoms; and

the groups R^{22} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or two of the groups R^{19}, together with the nitrogen to which they are attached, form a heterocyclic ring of from 5 to 7 atoms, or the three group R^{22} together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring.

The mole ratio of zwitterionic monomer to aromatic group containing monomer is generally in the range 1:99 to 99:1, preferably 1:20 to 1:1, more preferably in the range 1:10 to 1:2. The amount of zwitterionic monomer in total monomer is preferably in the range 1 to 95%, more preferably 5 to 50%, most preferably 10 to 25%. The amount of aromatic group containing monomer is preferably in the range 10 to 99%, more preferably 50 to 95%, most preferably 75 to 90%.

In the polymerisation mixture, the crosslinking monomer is generally present in a molar amount in the range 0.01% to 10%, most preferably in the range 0.1 to 5% based on total moles of monomer. Where a mixture of aromatic group containing cross-linking monomer to aliphatic group containing monomer is used the molar ratio of the two is preferably in the range 10:1 to 1:10, preferably 5:1 to 1:5, more preferably 2:1 to 1:2 most preferably 3:2 to 2:3.

The zwitterionic group containing monomer is generally included in sufficient levels to render the polymer swellable in water and to render the hydrogel more biocompatible.

According to a further aspect of the invention, there is provided a hydrogel formed of the novel crosslinked polymer and, dispersed throughout the polymer, an aqueous liquid. The water content of the polymer when fully swollen in deionised water is preferably in the range 10 to 50%, for instance in the range 20 to 40%, most preferably in the range 25 to 35%.

Preferably the hydrogel (the polymer swollen in water) is transparent. It is found that the hydrogel of the invention has a high transmission rate for visible light. The average transmission rate should preferably be above 90% throughout the range of visible light, 400 to 700 nm wavelengths.

The incorporation of the aromatic monomer enables high refractive indices to be achieved. Thus the refractive index of the fully water swollen hydrogel, may be at least 1.45, for instance up to 1.60. Preferably the refractive index is in the range 1.45 to 1.55.

The present invention includes also a polymerisation process, in which the mixture of monomers a, b and c are subjected to conditions whereby polymerisation is initiated and propagated. Initiation may be by any suitable means, for instance using thermal, redox or UV initiators, optionally in combination with one another. The polymer of the invention, when used as an intraocular lens, may include an absorber of ultraviolet light.

Since the zwitterionic monomer tends to be very polar and aromatic monomers tend to be non polar, the monomers may be immiscible with one another. In order to achieve a homogenous polymerisation mixture therefore it may be necessary to include a non polymerisable diluent liquid which acts as a common solvent for the monomers. A suitable solvent is an alcohol. The solvent is generally removed from the product

polymer after polymerisation, for instance by evaporation or by solvent replacement using an alternative liquid, generally water or other aqueous solution.

It is generally necessary to include any non polymerisable liquid diluent in an amount in the range 5 to 90% by weight based on the total weight of the polymerisation mixture. In order to avoid unnecessary solvent removal, the level is preferably less than 75%, for instance less than 50%. It is generally necessary to include at least 10% to achieve adequate dissolution of the monomers.

The polymerisation is generally conducted in some form of mould, for instance to form precursor products from which shaped lenses may be formed. Where such products are for instance rods, buttons or other lens precursors, shaping to form appropriate three dimensional shapes is generally by lathing. In order for lathing to take place, it is generally necessary to remove any polymerisation diluent prior to carrying out the lathing step.

Alternatively the lens or other final product may be polymerised in a mould of the desired final shape. In this case, the solvent is removed after polymerisation, for instance by solvent replacement.

For any polymerisation method, a final step in the formation of a hydrogel product involves swelling the crosslinked polymer in an aqueous liquid. The materials, when swollen in water have very desirable mechanical properties, for instance enabling them to be used as foldable IOL's. The strain at break for the swollen materials may be at least 50%, or even more than 100%. The modulus should preferably be in the range 1 to 4 MPa.

The materials (xerogels) have hardness values high enough to render them suitable for shaping by machining, for instance, by lathe cutting.

The product is found to have very desirable mechanical, optical and biocompatible properties rendering it suitable for use as a refractive device. The polymers are of particular value for use as intraocular devices especially intraocular lenses (IOL's) such as replacement lenses, lenses to augment the natural lens, e.g. posteria chamber phakic IOL's, anterior chamber phakic IOL's, corneal implants such as corneal inlays, corneal onlays and intracorneal rings.

The improved biocompatibility resulting from the incorporation of a zwitterionic monomer is believed to result in less damage being caused by a phakic lens on the natural

lens (avoiding cataract formation) or on the iris by chafing. For any intraocular device the improved biocompatibility should result in reduced inflammatory response. The results presented hereinafter show that the materials cause less endothelial damage than prior art materials.

The following examples illustrate the invention.

Abbreviations

EWC	=	Equilibrium Water Contact
RI	=	Refractive Index
Trans	=	Optical transmission
BA	=	Benzyl acrylate
HEMA-PC	=	2-Methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt
LM	=	Lauryl Methacrylate
EGDMA	=	Ethylene glycol dimethacrylate
BADMA	=	Bisphenol-A dimethacrylate
FEM	=	Fluoroethyl Methacrylate
AIBN	=	Azoisobutyronitrile

General polymerisation method

The monomers, including the crosslinking monomer, in the desired quantities, were dissolved in dry ethanol, in an amount of 20% (based on total polymerisation mixture weight) unless otherwise specified. Initiator of the desired type and in the desired amount was dissolved into the mixture (AIBN, unless otherwise specified). The liquid polymerisation mixture was thoroughly degassed using nitrogen. The polymerisation mixture was then injected into the desired mould (to form a membrane or button, as the case may be) which had previously been flushed with nitrogen. The mould was subsequently sealed and suspended in a water bath (containing oxygen scavenger) at the desired temperature (usually 60°C) for the desired period (usually sixteen hours) to complete polymerisation. Unless otherwise specified, the polymer, still in the mould after removal from the water bath, was annealed under vacuum at 90°C for a further sixteen hours, before being removed from the moulds. For all button

polymerisations, the buttons, after removal from the mould, were annealed at 110°C under vacuum for 4 days.

Mechanical Properties

EWC

The EWC is measured by weighing hydrogel lenses in their fully hydrated state and after drying in an oven overnight at 110 C.

Refractive Index

The retractive index is measured on an Atago device with the material in fully swollen (in water) form..

Hardness

The hardness of the F-type button (from which a lens is cut) is measured using a Type D Shore Durometer. A cross section is cut from the button using a microslicer or lathe and the centre and edge hardness recorded. This test is carried out on the xerogel.

Expansion Factor

This is determined from the ratio of diameter of lens hydrated to diameter of lens dry.

Tensile Properties

The mechanical analysis is carried out as a tensile test using a Mini Instron 44, using a 5 load cell at a speed of 5mm per minute. The material is tested at 25 +/- 2°C and kept hydrated throughout the test.

Biological Properties

The following tests are carried out on disks cut from polymer membranes, unless otherwise specified.

Fibrinogen Adhesion

This assay quantifies protein deposited on a test surface using polycolonal anti serum and enzyme-conjugated secondary anti serum. It provides a useful assessment of haemocompatibility and general biocompatibility.

Buttons of test material are each placed into a well of a twenty four well plate. One microgram fibrinogen in 50µl PBS. The fibrinogen solution is left in contact with the samples for two hours at room temperature. Subsequently the samples are washed three times with PBS, excess binding sites are blocked by overnight incubation with 4%

bovine serum albumin in PBS at 4°C. The buttons are subsequently washed three times with PBS and replaced into fresh wells of a new 24 well plate. 500µl diluted antithuman fibrinogen antiserum (1:1000 in PBS) is added and incubated with the samples for 30 minutes at room temperature. The buttons are washed three times in PBS and placed into fresh wells of a 24 well plate. 500µl diluted horseradish peroxidase-conjugated rabbit anti-goat antiserum (1:500 in PBS) is added and incubated for 30 minutes at room temperature. The buttons are washed three times in PBS and placed into fresh wells of a further 24 well plate. A substrate for the peroxidase enzyme is subsequently added in an appropriate buffer after contact with the samples for 10 minutes at room temperature. A terminator is added and the solutions read in a suitable colour remitter. The results are reported in terms of relative light units as compared to PMMA and pHEMA controls. High values thus correspond to high levels of adhesion.

Bacterial Adhesion Assay

This assay measures the bacterial (*Staphylococcus epidermidis*) attachment on the test materials using extraction of cellular ATP of attached bacterial cells. Extracted ATP is evaluated using bioluminescent technique. If bacteria adhere to and are carried with an intraocular lens into the eye, they could cause an infection.

Samples of the material under test are placed in the desired number of wells in a microtitre plate. A bacterial suspension at 3 x 10^8 CFU per ml in phosphate buffered saline is incubated in the wells for four hours at 37°C under agitation. The bacterial suspension is aspirated from the wells and samples subsequently rinsed in sterile phosphate buffered saline before being placed into the wells of a new plate. Lysis buffer (0.1% trichloroacetic acid, 1% xylenol 2mM EDTA in deionised water) is placed into the well and left in contact with the sample for 10 minutes to extract the ATP. Extracted ATP is diluted with tris acetate buffer 1:1, ATP monitoring reagent is added and light emission determined in a bioluminescent plate reader. Bioluminessence is related to a number of bacterial cells by generating a calibration curve.

Fibroblast Adhesion Assay

This assay determines the adhesion of a standard adherent cell line, mouse 3T3 fibreblasts, in tissue culture medium, to samples on the test.

The fibroblast cells are cultivated in a tissue culture step to confluent or near confluent monolayer. The monolayer is detached from the flask using a solution of

trypsin-EDTA, and subsequently suspended in serum-containing medium. Test disks of the material under test of 13mm diameter are placed into twenty four well plates. 0.5mls of cell suspension (having a cell concentration of 3000 per ml) is added and incubated for 72 hours at 37°C. The samples are removed from the wells and washed with PBS. The samples with adherent cells are placed into wells of a new plate and subjected to lysis for 30 minutes at room temperature followed by freezing overnight. After addition of further lysis buffer, ATP monitoring reagent is added to the wells and luminescence subsequently read to determine ATP levels. The results are reported in terms of relative light units as compared to standard materials (polymethylmethacrylate and polyhydroxyethylmethacrylate).

Granulocyte Activation

This method measures granulocyte activation in response to superoxide radicals by disks of materials under test. It is a useful measure of biocompatibility. The cells subjected to the test are polymorphonuclear leucocytes (PMN's) from venus blood. Incubation of the cells in the presence of the materials under test is conducted in the presence of nitroblue tetrazolium, which detects the oxidative burst triggered by inflammatory materials upon granulocyte activation to be visualised colorimetrically.

PMN's are separated from venus blood using a suitable technique. They are suspended in Earl's salt solution containing 10% foetal calf serum at a cell density of 1 x 10^6 cells per ml. 100µl of the cell suspension is contacted with 13mm disks of samples under test in the wells of a microtitre plate. After 30 minutes at 37°C, the samples in the wells are washed three times with phosphate buffered saline and then 100µl of nitroblue tetrazolium is added to the wells. Adherent cells are incubated with the NBT solution for at least one hour at 37°C. Subsequently cells are fixed using formaldehyde, washed and viewed under light microscopy. Activated granulocytes appear blue. The number of activated granulocytes as compared to polymethylmethacrylate controls and positive controls (polymethylmethacrylate treated with phorbol ester as a positive control).

Macrophage Adhesion

This protocol measures macrophage adhesion to test surfaces, another useful measure of biocompatibility. The protocol involves incubation with novel materials

overnight which exploits the known tendency of macrophages to attach to plastics surfaces.

Suitable purification steps are conducted to separate out mononuclear cells from venus blood. The cells are suspended in serum-free macrophage medium (commercially available) at a concentration of 10^6 cells per ml. 200µl of medium is added to wells of a microtitre plate containing 13mm diameter disks of materials under test. The plates are left overnight at 37°C after which disks are moved to a new plate and washed three times before fixing with formaldehyde and staining with Dako anti-macrophage antibody-biotin conjugate. Attached antibody is subsequently visualised using a Sigma high intensity rapid stain kit containing an avidin-peroxidase conjugate with 3-amino-9-ethyl carbazole (AEC) as chromogen. The numbers of macrophages is determined using light microscopy and compared against controls.

Rabbit epithelial lens cell adhesion

AGO4677, a mortal primary rabbit lens epithelial cell strain was obtained from the National Institute of Aging (NIA) repository (Cambden, NJ, USA). The cells were cultures in Minimal Essential Eagles Medium (MEM) with double the normal concentration of non-essential amino acids (Gibco) and 10% (v/v) foetal calf serum (FCS) at a density of 6000 cells cm^{-2} at 37°C in 5% CO_2. The cells were never permitted to become confluent under maintenance conditions and were passaged by routine trypsin dispersion. Adhesion of the AGO4677 was assayed by ATP extraction 72 h after 1000 viable rabbit lens cells were plated onto discs of material. ATP was liberated by incubating each disk with 100 µl of a sterile hypotonic lysis buffer (0.01M Tris-Acetate pH 8, 2 mM EDTA). The ATP solution was then diluted 1:1 with a commercial assay buffer designed for ATP luminometry (0.1 M Tris-Acetate pH 8, 2 mM EDTA) and the amount of ATP in each sample measured using a commercial kit (BioOrbit-Wallac, Turku Finland) and a 96 well plate luminometer (Amerlite, Amersham).

Corneal Endothelial Cell Touch Test

This test method is a highly discriminating assay for intraocular lens utility. The test involves contacting materials under test with a confluent monolayer of bovine corneal endothelium (BCE) cells for a predetermined period of time and qualitatively assessing the damage to the monolayer.

Confluent monolayers of BCE cells in sterile tissue culture dishes are established by culturing in the presence of dulbecco's modified eagles medium (DMEM) containing foetal bovine serum, new born calf serum, penicillin and streptomycin. The monolayers were rinsed to remove unattached cells. A sterile 13mm disk of test sample (xerogel) is rinsed ten times with sterile PBS to hydrate. The hydrated disk is then placed on the BCE monolayer surface and a weight placed upon the top of a disk to ensure contact (in the "Av Damage", and HamaIP tests (see Table 7) a 2g weight was used, whilst a lighter weight was used for the "cell damage" results). After a predetermined period of time (3½ minutes) the disk is removed, fresh medium is added and the cells incubated for 15 minutes to allow recovery. The cells are then viewed under inverted light microscope and the damage is qualitatively assessed on a numerical scale of 0 (complete destruction) to 10 (minimal damage). Values are given as Av(erage) Damage in results. The cells are also analysed by fixing, staining with Harris hematoxylin solution and viewed using Argus 50 software and a Hamamatsu image processor (Hama IP). The results of the quantitative determination are expressed in terms of mean percent damage (sample number six).

Example 1

Polymerisations were conducted to form membranes using the general polymerisation method between two glass plates lined with PET and separated by a PTFE spacer using azoisobutyronitrile and 20 weight % ethanol. The effect of including diluent monomer, lauryl methacrylate or fluoroethylmethacrylate, was investigated in these experiments. The monomers, and their proportions are shown in Table 1, as are the results of performing test methods for RI, EWC and visible light transmission at 700 nm and 480 nm on polymer fully swollen in water.

Table 1

Example	Mole %						Properties			
	BA	HEMA-PC	LM	FEM	BADMA	EGDMA	RI	700nm	480nm	EWC
1.1.1	83	15	0	0	1	1	1.4555	94.5	89.26	37.6
1.1.2	83	15	0	0	0.75	1.25	1.4585	94.79	89.9	37.7
1.1.3	83	15	0	0	0.5	1.5	1.451	94.87	89.58	39.6
1.1.4	79	15	0	0	1	5	1.4805	95.66	93.69	29.9
1.2.1	78	15	0	5	1	1	1.4565	-	-	38.2
1.2.2	73	15	0	10	1	1	1.452	-	-	38.1
1.2.3	63	15	0	20	1	1	1.447	-	-	37.3
1.2.4	53	15	0	30	1	1	1.4405	-	-	38.1
1.3.1	83	15	0	0	1	1	1.462	89.15	82.54	37.9
1.3.2	78	15	5	0	1	1	1.459	87.46	81.31	35.7
1.3.3	73	15	10	0	1	1	1.454	86.31	77.2	36.3
1.3.4	63	15	20	0	1	1	1.4505	90.18	82.99	35.0
1.3.5	53	15	30	0	1	1	1.446	93.31	88	31.8
1.3.6	43	15	40	0	1	1	1.483	94.31	88.01	29.7
1.4.1	73.5	15	10	0	1	0.5	1.454	88.2	81.38	37.0

Table 1 (cont)

Example	Mole %						Properties			
	BA	HEMA-PC	LM	FEM	BADMA	EGDMA	RI	700nm	480nm	EWC
1.4.2	63.5	15	20	0	1	0.5	1.46	91.34	84.72	36.2
1.5.1	83.5	15	0	0	0.5	1	1.449	81.68	74.37	42.6
1.5.2	83	15	0	0	1	1	1.457	86.28	81.85	38.4
1.5.3	82	15	0	0	2	1	1.4715	76.84	72.11	33.2
1.5.4	84	15	0	0	1	0	1.465	93.87	91.48	35.8
1.5.5	83.5	15	0	0	1	0.5	1.4485	89.59	83.98	40.6
1.5.6	82	15	0	0	1	2	-	91.63	84.81	41.0
1.6.1	83	15	0	0	1	1	1.454	85.98	81.01	39.1
1.6.2	78	15	5	0	1	1	1.4535	87.31	81.41	39.2
1.6.3	73	15	10	0	1	1	1.454	85.73	78.63	38.2
1.6.4	78	15	0	5	1	1	1.4525	85.94	79.45	39.6
1.6.5	73	15	5	5	1	1	1.4525	86.82	79.85	38.3
1.7.1	83	15	0	0	1	1	1.456	96.55	93.76	-
1.7.2	73	15	10	0	1	1	1.459	-	-	33.7
1.7.3	85.5	12.5	0	0	1	1	1.469	95.82	92.58	-

Table 1 (cont)

Example	Mole %						Properties			
	BA	HEMA-PC	LM	FEM	BADMA	EGDMA	RI	700nm	480nm	EWC
1.7.4	75.5	12.5	10	0	1	1	-	-	-	30.4
1.7.5	88	10	0	0	1	1	1.488	95.84	92.75	-
1.7.6	78	10	10	0	1	1	1.485	93.32	88.57	23.7

The results show that high refractive index, optically clear materials can be formulated from monomers including HEMA-PC. These are expected to have improved biocompatibility compared to comparative materials not comprising pendant zwitterionic groups.

The results also show that, with the same weight proportion of HEMA-PC, replacing increasing levels of benzylmethacrylate with aliphatic diluent monomer results in a decrease in RI, with a similar level of charge resulting from such replacement by lauryl methacrylate or fluoroethyl methacrylate. Increasing the total level of crosslinker results in a decrease in the EWC with a corresponding increase in RI. The copolymers appear to have better transmission rates for visible light than the terpolymers. Reducing the level of HEMA-PC results in a reduction of EWC, and an increase in RI.

Example 2

Further polymerisations to form membranes were conducted using the general method, to investigate the effect on the EWC, RI and transmission, and also the mechanical characteristics and biocompatibility, of changing the relative amounts of zwitterionic and aromatic group containing monomer. The biocompatibility is, in this experiment determined using the fibrinogen adsorption test described above, the control being a polymer of 98% mole benzyl methacrylate and 1% each (mole) of EGDMA and BADMA crosslinker. The monomer proportions are shown in Table 2. The results are shown in Table 3. The results show that the strain for materials formed from monomers including lauryl methacrylate in place of benzylacrylate is reduced. The results of example 2.1-2.5 show that polymers having PC groups can be formed with good mechanical and optical properties and which have good biocompatibility as adjudged by the reduction of fibrinogen adsorption.

Table 2

Example	Mole % Monomers		
	BA	**HEMA-PC**	**LM**
2.1	83	15	0
2.2	85.5	12.5	0
2.3	88	10	0
2.4	90.5	7.5	0
2.5	83	15	0
2.6	73	15	10
2.7	63	15	20
2.8	53	15	30
2.9	43	15	40
2.10	33	15	50

Table 3

Example	EWC	RI	Trans/ 700nm %	Trans. 480nm %	Modulus MPa	Tensile Strain %	Strength MPa	Fibr.gn. Redn.%
2.1	38.3	1.450	92.25	87.31	1.312	81.8	0.740	73
2.2	32	1.461	93.18	87.36	1.773	67	0.758	79
2.3	27.6	1.480	93.22	87.96	1.870	116.7	1.399	83
2.4	26.8	1.488	93.12	88.04	2.109	142.5	1.932	76
2.5	38.8	1.459	91.43	86.11	0.814	63.8	0.560	74
2.6	35.1	1.460	90.87	85.93	0.914	56.7	0.600	72
2.7	32.4	1.461	91.03	85.99	1.064	45.1	0.549	77
2.8	32.2	1.451	90.45	86.14	1.043	42.2	0.544	67
2.9	29.0	1.452	90.63	86.05	1.063	40.2	0.499	77
2.10	27.5	1.454	90.73	85.87	0.984	45.1	0.573	74

Example 3

Polymerisations in button moulds

In this and the following exxample the effects of changing the type of cross-linker, the level of initiator and the level of solvent on optical and mechanical properties are investigated.

Monomers at the mole proportions shown in Table 5 were polymerised by the general method. All polymerisation contained 15 mole % HEMA-PC and the remaining amount after taking the cross-linker quantities into consideration was BA. The EF, hydrated optical clarity, EWC and hardness of the variant buttons are shown in Table 5.

Table 4

Example No.	EGDMA Level /mol%	BADMA Level /mol%	AIBN Level /mole %	Comments
3.1	0	2	0.25	-
3.2	2	0	0.25	-
3.3	2	0	0.05	-
3.4	2	0	1.0	-
3.5	1.5	0.5	0.25	-
3.6	1	1	0.05	-
3.7	1	1	0.05	Repeat of 3.6
3.8	1	1	0.25	15 wt% ethanol
3.9	1	1	0.25	-

Table 5

Example	Appearance	Other	Expansion Factor	Hydrated Optical Clarity	EWC	Hardness
3.1	Buttons turned white due to phase separation	-	x	x	x	x
3.2	Clear buttons, did not shatter on annealing	-	1.16±0.03	clear	34.8±0.1	72±0.5
3.3	Clear buttons, crazed effect on top surface	-	1.16±0.03	clear	35.0±0.0	66±1.1
3.4	Buttons turned white due to phase separation	-	x	x	x	x
3.5	Clear buttons	-	1.15±0.03	clear	32.3±0.0	71±0.8
3.6	Clear buttons, crazed effect on top surface	-	1.13±0.01	clear	30.6±0.2	78±.08
3.7	Clear buttons, crazed effect on top surface	Repeat of 3.6	1.14±0.03	clear	30.5±0.0	68±1.6
3.8	Clear buttons. Turn slightly opaque on hydrating	15 wt% ethanol	1.12±0.04	Slightly opaque	29.7±0.0	78±0.6
3.9.1	Clear buttons	-	1.11±0.02	clear	29.7±0.1	66±0.6
3.9.2		-	1.13±0.03	clear	30.7±0.0	78±0.5
3.9.3		-	1.13±0.01	clear	31.5±0.1	74±0.5
3.9.4		-	1.13±0.02	clear	31.6±0.1	82±0.5

x - not tested

Example 4

Slices of some of the buttons made in Example 3 were subjected to mechanical tests to give the results shown in Table 6.

Table 6

Sample	Variant			Mechanical Properties		
	EGDMA level mole %	BADMA level mole %	AIBN level mole %	Modulus MPa	Stress MPa	Strain %
3.9.3	1	1	0.25	1.73±0.89	0.89±0.06	80.40±17.25
3.5	1.5	0.5	0.25	0.97±0.04	0.61±0.06	69.75±5.57
3.2	2	0	0.25	0.70±0.13	0.60±0.05	102.98±3.58
3.3	2	0	0.05	0.53±0.26	0.51±0.04	91.72±14.09
3.6	1	1	0.05	1.16±0.11	0.79±0.01	77.59±17.56

Discussion of Example 3 and 4

Crosslinker

The standard formulation HEMA-PC:BA:EGDMA:BADMA 15:83:1:1 was altered to use only one crosslinker, 2 mol% EGDMA or 2 mol% BADMA. The production of 2% BADMA was unsuccessful resulting in white soft buttons due to phase separation. The complete removal of EGDMA from the polymer is unfavourable, as it seems to result in a loss of clarity.

Decreasing the level of BADMA from 2 to 0 mol%, and increasing the EGDMA level to maintain 2 mol% crosslinker level overall, results in buttons which have a higher expansion factor, higher water content and therefore reduced mechanical properties. This trend is shown clearly in Table 5 and 6 . Increasing the EGDMA level at the expense of BADMA increases the water content due to the hydrophobic nature of BADMA.

Reducing solvent level

In the general method 20 wt% solvent was incorporated into the formulation to make the monomers miscible with each other. Example 3.8 was carried out to examine the effect of reducing the ethanol level to just above the lowest miscible level, 15 wt%. This would reduce the time required to remove the solvent from the buttons before lathing. From Table 5 it was shown that the hydrated buttons are slightly opaque.

Example 5

Lenses were cut from some of the buttons produced in example 3.6 by lathe to a parallel mono-curve design, 0.25mm thick. The lenses, prior to hydration, had a gem-like quality, equivalent to polymethylmethacrylate. The lenses were hydrated and subjected to mechanical testing. The hydrated lenses were tested to have a modulus of 1.508 ± 0.125 MPa, stress of 2.282 ± 0.442 MPa and strain $102.93 \pm 15.30\%$.

The mechanical properties of the lenses are better than button slices of the same formulation. These differences may arise from the different dimension sizes of test samples (lens 0.25 mm thick compared to slices 1.50 mm thick).

Example 6

Further membrane polymerisations were conducted using the monomer mixtures shown in table 7. For all examples, the initiator level was 0.25 mole % AIBN, whilst 1 mole % mole of EGDMA and BADMA were included as crosslinkers. The aromatic

group containing comonomer used was BA in each case and that comonomer made up the remaining monomer in the polymerisation mixture. 20 weight % ethanol (based on the total polymerisation mixture) was used as solvent. The level of HEMA-PC was as specified in the table.

Discs cut from the membrane were subjected to biological evaluations. The results of the fibrinogen adsorption, fibroblast adhesion assay, bacterial adhesion assay, macrophage adhesion assay, granulocyte activation assay and bovine corneal endothelial touch test are shown in table 7. The results show that high R1 materials (see examples 1 and 2) which are biocompatible. In combination with example 2, these results show that biocompatible materials can be formulated with a range of mechanical properties appropriate for different applications and lens designs.

Example 7

In vivo experiments were conducted in which lenses of the composition of example 3.9 lathe cut from buttons were implanted into rabbits using conventional equipment for insertion of IOL's in a rolled conformation. The results were successful.

The lenses were each circular and had a refractive power of about -12D in the eye. One type of lens had a diameter of 9mm and centre thickness of 0.6mm, whilst the other had a diameter of 7mm and a centre thickness of 0.2mm.

Example 8

The formulation of example 3.6 was prepared but with 1% (by weight) of Daracure 1173 (CIBA GEIGY) as photoinitiator instead of AIBN, and 30% by weight of ethanol. Aliquots of the formulation were placed in circular lens molds machined from polymethylpentene (TPX, Goodfellows). The molds were sealed and subjected to ultraviolet irradiation for 1 hour (mid range UV). The cured lenses were removed and extracted with ethanol and then water. The resulting lenses were clear and had a refractive index of 1.48. In the BCE assay (using the lighter weight) their performance was almost equivalent to that of the machined lenses (average score 8 versus control 10 and lathed 9.5).

Table 7

Example	mole % HEMA-PC	Fib'n Ads'n Rel.Abs.	Fibroblast Ad'n RLU	Bact. Ad'n RLU	Epi Ad'n RLU	M'phage Ad'n RLU	G'cyte Act'n Av no.	BCE		Cell Damage
								Av Damage (2g)	Hama IP	
6.1 (2.1)	15	0.0	7	0.4	3	0.1	0.7	8	0.02	2
6.2 (2.2)	12.5	0.2	15	2.1	4	1.6	2.9	NT	0.02	3
6.3 (2.3)	10	0.0	17	3.5	5	2.3	1.8	NT	NT	2
6.4 (2.4)	7.5	0.5	8	5.3	6	0.2	4.7	NT	NT	4
6.5 lathed	15							9.5	NT	NT
PMMA Control	-	2.0	34	11.7	47	10.6	7.5	3	1.5	9
PHEMA Control	-	0.2	40	3.5	19	0.5	6.8	6	0.53	4

CLAIMS

1. A crosslinked polymer obtainable by radical polymerisation of ethylenically unsaturated monomers including

a) a zwitterionic monomer of the general formula I

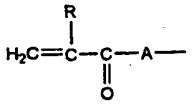
YBX I

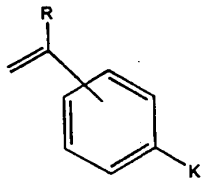
wherein

B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X or Y contains a terminal carbon atom bonded to B, a valence bond;

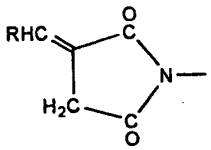
X is a zwitterionic group; and

Y is an ethylenically unsaturated polymerisable group selected from

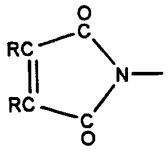




CH_2=C(R)-CH_2-O-, CH_2=C(R)-CH_2 OC(O)-, CH_2=C(R)OC(O)-, CH_2=C(R)-O-, CH_2=C(R)CH_2OC(O)N(R^1)-, R^2OOCCR=CRC(O)-O-, RCH=CHC(O)O-, RCH=C(COOR^2)CH_2-C(O)-O-,



and



wherein:

R is hydrogen or a C_1-C_4 alkyl group;

R^1 is hydrogen or a C_1-C_4 alkyl group or R^1 is -B-X where B and X are as defined above; and

R^2 is hydrogen or a C_{1-4} alkyl group or BX where B and X are as defined above;

A is -O- or -NR^1-;

K is a group -$(CH_2)_p$OC(O)-, -$(CH_2)_p$C(O)O-,

-$(CH_2)_p$OC(O)O-, -$(CH_2)_p$$NR^3$-, -$(CH_2)_p$$NR^3$C(O)-,

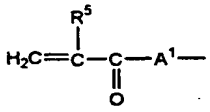
-$(CH_2)_p$C(O)NR^3-, -$(CH_2)_p$$NR^3$C(O)O-, -$(CH_2)_p$OC(O)$NR^3$-,

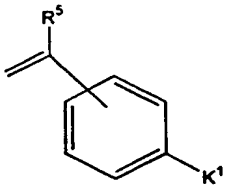
$-(CH_2)_pNR^3C(O)NR^3-$ (in which the groups R^3 are the same or different), $-(CH_2)_pO-$, $-(CH_2)_pSO_3-$, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R^3 is hydrogen or a C_1-C_4 alkyl group.

b) an aromatic group containing monomer of the general formula II

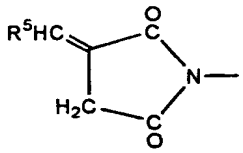
$$Y^1R^4 \qquad II$$

wherein Y^1 is selected from

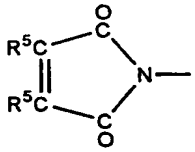




$CH_2=C(R^5)-CH_2-O-$, $CH_2=C(R^5)-CH_2\ OC(O)-$, $CH_2=C(R^5)OC(O)-$, $CH_2=C(R^5)-O-$, $CH_2=C(R^5)CH_2OC(O)N(R^6)-$, $R^7OOCCR^5=CR^5C(O)-O-$, $R^5CH=CHC(O)O-$, $R^5CH=C(COOR^7)CH_2-C(O)-O-$,



and



wherein:

R^5 is hydrogen or a C_1-C_4 alkyl group;

R^6 is hydrogen or a C_1-C_4 alkyl group or R^5 is R^3; and

R^7 is hydrogen or a C_{1-4} alkyl group or R^3

A^1 is -O- or $-NR^6-$;

K^1 is a group $-(CH_2)_qOC(O)-$, $-(CH_2)_qC(O)O-$,

$-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^8-$, $-(CH_2)_qNR^8C(O)-$,

$-(CH_2)_qC(O)NR^8-$, $-(CH_2)_qNR^8C(O)O-$, $-(CH_2)_qOC(O)NR^8-$,

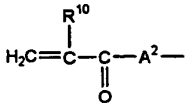
$-(CH_2)_qNR^8C(O)NR^8-$ (in which the groups R^8 are the same or different), $-(CH_2)_qO-$, $-(CH_2)_qSO_3-$, or a valence bond and p is from 1 to 12 and R^8 is hydrogen or a C_1-C_4 alkyl group;

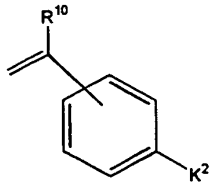
and R^4 is an aromatic group; and

c) a cross-linking monomer of the general formula III

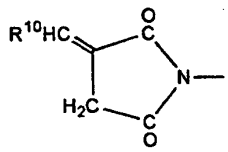
$$(Y^2)_nR^9 \qquad III$$

in which n is an integer of at least 2, each Y^2 is selected from

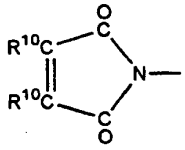




$CH_2=C(R^{10})-CH_2-O-$, $CH_2=C(R^{10})-CH_2OC(O)-$, $CH_2=C(R^{10})OC(O)-$, $CH_2=C(R^{10})-O-$, $CH_2=C(R^{10})CH_2OC(O)N(R^{11})-$, $R^{12}OOCCR^{10}=CR^{10}C(O)-O-$, $R^{10}CH=CHC(O)O-$, $R^{10}CH=C(COOR^{12})CH_2-C(O)-O-$,



and



wherein:

R^{10} is hydrogen or a C_1-C_4 alkyl group;

R^{11} is hydrogen or a C_1-C_4 alkyl group or R^{11} is R^4; and

R^{12} is hydrogen or a C_{1-4} alkyl group or R^3

A^2 is -O- or $-NR^{11}-$;

K^2 is a group $-(CH_2)_rOC(O)-$, $-(CH_2)_rC(O)O-$, $-(CH_2)_rOC(O)O-$, $-(CH_2)_rNR^{12}-$, $-(CH_2)_rNR^{12}C(O)-$, $-(CH_2)_rC(O)NR^{12}-$, $-(CH_2)_rNR^{12}C(O)O-$, $-(CH_2)_rOC(O)NR^{12}-$, $-(CH_2)_rNR^{12}C(O)NR^{12}-$ (in which the groups R^{12} are the same or different), $-(CH_2)_rO-$, $-(CH_2)_rSO_3-$ or a valence bond and r is from 1 to 12 and R^{12} is hydrogen or a C_1-C_4 alkyl group;

and R^9 is an n-functional organic group.

2. A polymer according to claim 1 in which R^4 is benzyl or phenyl.

3. A polymer according to any preceding claim in which Y and Y^2 are the same, and are preferably $CH_2=CR^xCOA$, in which R^x is R and R^{10} and is methyl or hydrogen and A is O.

4. A polymer according to any preceding claim in which R^9 is an aromatic group preferably a bis-phenol A group.

5. A polymer according to any preceding claim which includes a crosslinking agent in which R^9 is an aliphatic group, preferably an ethylene or an oligo(ethyleneoxy)ethylene group.

6. A polymer according to any of claims 1 to 3 in which the monomers include a mixture of at least two cross-linking monomers of the general formula III, in at least one of which R^9 is an aromatic group, preferably a bisphenol A group, and at least one of which R^9 is an aliphatic group, preferably an ethylene or oligo (ethyleneoxy)ethylene group.

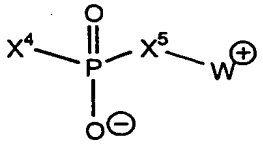
7. A polymer according to claim 6 in which the molar ratio of crosslinking monomer in which R^9 is aromatic to crosslinking monomer in which R^9 is aliphatic is in the range 10:1 to 1:10, preferably 5:1 to 1:5, most preferably 2:1 to 1:2.

8. A polymer according to any preceding claim in which the zwitterionic monomer is present in molar amount in the range 1 to 95%, preferably 5 to 50%, more preferably 10 to 25%, based on total ethylenically unsaturated monomer.

9. A polymer according to any preceding claim in which the aromatic group containing monomer is present in a molar amount in the range 10 to 99%, preferably 50 to 95%, more preferably 75 to 90%, based on total ethylenically unsaturated monomer.

10. A polymer according to any preceding claim in which the crosslinking monomer is present in a molar amount in the range 0.01 to 10%, preferably 0.1 to 5%, more preferably in the range 0.5 to 3% based on total ethylenically unsaturated monomer.

11. A polymer according to any preceding claim in which the zwitterionic group has the general formula IV



IV

in which the moieties X^4 and X^5, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C_{1-12}-alkylene group,

preferably in which W^+ is a group of formula

$-W^1-N^+R^{14}_3$, $-W^1-P^+R^{15}_3$, $-W^1-S^+R^{15}_2$ or $-W^1-Het^+$ in which:

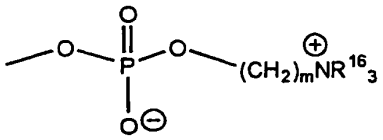
W^1 is alkylene of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl, alkylene aryl, aryl alkylene, or alkylene aryl alkylene, disubstituted cycloalkyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R^{14} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl or two of the groups R^{14} together with the nitrogen atom to which they are attached form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{14} together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^{14} is substituted by a hydrophilic functional group, and

the groups R^{15} are the same or different and each is R^{14} or a group OR^{14}, where R^{14} is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine,

12. A polymer according to claim 11 in which X is a group of formula V:



V

where the groups R^{16} are the same or different and each is hydrogen or C_{1-4} alkyl, and

m is from 1 to 4,

in which preferably the groups R^{16} are the same.

13. A gel comprising a polymer according to any preceding claim swollen by a liquid.

14. A gel according to claim 13 in which the liquid is aqueous.

15. A refractive device formed of a polymer according to any of claims 1 to 12.

16. A device according to claim 15 which has an average transmission for visible light in the range 400 to 700nm wavelength of at least 90% (when swollen by water).

17. A device according to claim 15 or claim 16 which comprises an absorber of electromagnetic radiation, preferably of U.V. light.

18. A device according to any of claims 15 to 17, having a refractive index when fully swollen in water in the range 1.45-1.60.

19. A polymerisation process in which a polymerisation mixture containing ethylenically unsaturated monomers is subjected to radical polymerisation, whereby addition polymerisation of the ethylenically unsaturated groups takes place, and in which the monomers include

a) a zwitterionic monomer of the general formula I

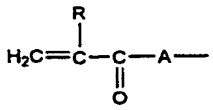
YBX I

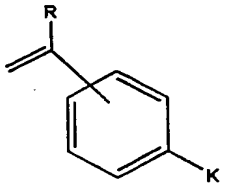
wherein

B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X or Y contains a terminal carbon atom bonded to B, a valence bond;

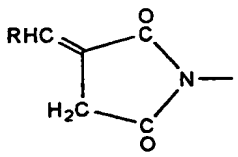
X is a zwitterionic group; and

Y is an ethylenically unsaturated polymerisable group selected from

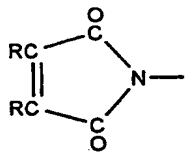




CH_2=C(R)-CH_2-O-, CH_2=C(R)-CH_2 OC(O)-, CH_2=C(R)OC(O)-, CH_2=C(R)-O-, CH_2=C(R)CH_2OC(O)N(R^1)-, R^2OOCCR=CRC(O)-O-, RCH=CHC(O)O-, RCH=C(COOR^2)CH_2-C(O)-O-,



and



wherein:

R is hydrogen or a C_1-C_4 alkyl group;

R^1 is hydrogen or a C_1-C_4 alkyl group or R^1 is -B-X where B and X are as defined above; and

R^2 is hydrogen or a C_{1-4} alkyl group or BX where B and X are as defined above;

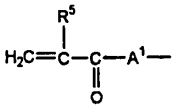
A is -O- or $-NR^1-$;

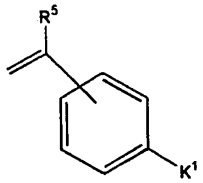
K is a group $-(CH_2)_pOC(O)-$, $-(CH_2)_pC(O)O-$,
$-(CH_2)_pOC(O)O-$, $-(CH_2)_pNR^3-$, $-(CH_2)_pNR^3C(O)-$,
$-(CH_2)_pC(O)NR^3-$, $-(CH_2)_pNR^3C(O)O-$, $-(CH_2)_pOC(O)NR^3-$,
$-(CH_2)_pNR^3C(O)NR^3-$ (in which the groups R^3 are the same or different), $-(CH_2)_pO-$,
$-(CH_2)_pSO_3-$, or, optionally in combination with B, a valence bond and p is from 1 to 12
and R^3 is hydrogen or a C_1-C_4 alkyl group.

b) an aromatic group containing monomer of the general formula II

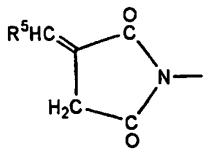
$$Y^1R^4 \qquad II$$

wherein Y^1 is selected from

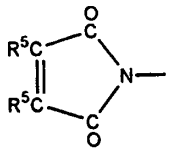




$CH_2=C(R^5)-CH_2-O-$, $CH_2=C(R^5)-CH_2\ OC(O)-$, $CH_2=C(R^5)OC(O)-$, $CH_2=C(R^4)-O-$,
$CH_2=C(R^5)CH_2OC(O)N(R^6)-$, $R^7OOCCR^5=CR^5C(O)-O-$, $R^5CH=CHC(O)O-$,
$R^5CH=C(COOR^7)CH_2-C(O)-O-$,



and



wherein:

R^5 is hydrogen or a C_1-C_4 alkyl group;

R^6 is hydrogen or a C_1-C_4 alkyl group or R^6 is R^4; and

R^7 is hydrogen or a C_{1-4} alkyl group or R^4

A^1 is -O- or $-NR^6-$;

K^1 is a group $-(CH_2)_qOC(O)-$, $-(CH_2)_qC(O)O-$,
$-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^8-$, $-(CH_2)_qNR^8C(O)-$,
$-(CH_2)_qC(O)NR^8-$, $-(CH_2)_qNR^8C(O)O-$, $-(CH_2)_qOC(O)NR^8-$,

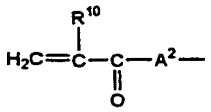
$-(CH_2)_qNR^8C(O)NR^8-$ (in which the groups R^8 are the same or different), $-(CH_2)_qO-$, $-(CH_2)_qSO_3-$, or a valence bond and p is from 1 to 12 and R^8 is hydrogen or a C_1-C_4 alkyl group;

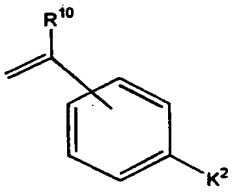
and R^4 is an aromatic group; and

c) a cross-linking monomer of the general formula III

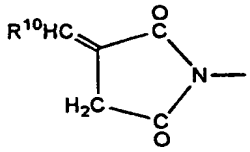
$$(Y^2)_nR^9 \qquad \text{III}$$

in which n is an integer of at least 2, each Y^2 is selected from

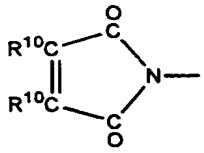




$CH_2=C(R^{10})-CH_2-O-$, $CH_2=C(R^{10})-CH_2\,OC(O)-$, $CH_2=C(R^{10})OC(O)-$, $CH_2=C(R^{10})-O-$, $CH_2=C(R^{10})CH_2OC(O)N(R^{11})-$, $R^{12}OOCCR^{10}=CR^{10}C(O)-O-$, $R^{10}CH=CHC(O)O-$, $R^{10}CH=C(COOR^{12})CH_2-C(O)-O-$,



and



wherein:

R^{10} is hydrogen or a C_1-C_4 alkyl group;

R^{11} is hydrogen or a C_1-C_4 alkyl group or R^{11} is R^4; and

R^{11} is hydrogen or a C_{1-4} alkyl group or R^3;

A^2 is -O- or $-NR^{11}-$;

K^2 is a group $-(CH_2)_rOC(O)-$, $-(CH_2)_rC(O)O-$,

$-(CH_2)_rOC(O)O-$, $-(CH_2)_rNR^{12}-$, $-(CH_2)_rNR^{12}C(O)-$,

$-(CH_2)_rC(O)NR^{12}-$, $-(CH_2)_rNR^{12}C(O)O-$, $-(CH_2)_rOC(O)NR^{12}-$,

$-(CH_2)_rNR^{12}C(O)NR^{12}-$ (in which the groups R^{12} are the same or different), $-(CH_2)_rO-$, $-(CH_2)_rSO_3-$ or a valence bond and r is from 1 to 12 and R^{12} is hydrogen or a C_1-C_4 alkyl group;

and R^9 is an n-functional organic group.

20. A process according to claim 19 in which the zwitterionic monomer is present in molar amount in the range 1 to 95%, preferably 5 to 50%, more preferably 10 to 25%, based on total ethylenically unsaturated monomer.

21. A process according to claim 19 or claim 20 in which the aromatic group containing monomer is present in a molar amount in the range 10 to 99%, preferably 50 to 95%, more preferably 75 to 90%, based on total ethylenically unsaturated monomer.

22. A process according to any of claims 19 to 21 in which the crosslinking monomer is present in a molar amount in the range 0.01 to 10%, preferably 0.1 to 5%, more preferably in the range 0.5 to 3% based on total ethylenically unsaturated monomer.

23. A process according to any of claims 19 to 22 in which polymerisation is initiated by a thermal, a redox or a U.V. initiator.

24. A process according to any of claims 19 to 23 in which the zwitterionic monomer and aromatic group containing monomer are immiscible in the absence of a co-solvent, and in which the polymerisation mixture contains a co-solvent which is a non-polymerisable liquid whereby the polymerisation mixture is a homogeneous solution.

25. A process according to claim 24 in which the co-solvent is an alcohol.

26. A process according to claim 24 or claim 25 in which the co-solvent is present in the polymerisation mixture in an amount in the range 5 to 90% by weight, preferably in the range 10 to 75%, more preferably 10 to 50% by weight.

27. A process of forming a refractive device in which a polymerisation process according to any of claims 24 to 26 is carried out, the co-solvent is removed from the product polymer and the xerogel which is substantially free of co-solvent is shaped by cutting to a predetermined three dimensional shape.

28. A process according to claim 27 in which the product is used as an intraocular lens.

29. A process of forming a refractive device in which a polymerisation process according to any of claims 24 to 26 is carried out whilst the polymerisation mixture is in a mould and, after polymerisation, the solvent is removed from the polymer, usually after removal from the mould, preferably by replacement with a second solvent.

30. A process according to any of claims 27 to 29 in which polymer product is water-swellable and the shaped or moulded product is swollen in aqueous liquid.

31. A process according to any of claims 19 to 30 having the further features defined in any of claims 2 to 7, 11 and 12.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
UNITED KINGDOM

Applicant's or agent's file reference HMJ02835WO	Date of mailing (day/month/year) 24/03/2000 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB 99/ 04206	International filing date (day/month/year) 13/12/1999
Applicant BIOCOMPATIBLES LIMITED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41–22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from th priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Philip Van Kalsbeek

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
HMJ02835WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 04206	13/12/1999	11/12/1998
Applicant		
BIOCOMPATIBLES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure N .

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
/GB 99/04206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08F246/00 G02B1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 485 197 A (NESTLE SA) 13 May 1992 (1992-05-13) cited in the application	
A	WO 92 07885 A (BIOCOMPATIBLES LTD.) 14 May 1992 (1992-05-14) cited in the application	
A	WO 92 11301 A (ALLERGAN INC.) 9 July 1992 (1992-07-09) cited in the application	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2000	24/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cauwenberg, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/GB 99/04206

Patent document cited in search report		Publication dat	Patent family member(s)		Publication date
EP 485197	A	13-05-1992	AT	143677 T	15-10-1996
			AU	652389 B	25-08-1994
			AU	8705091 A	14-05-1992
			CA	2055138 A,C	08-05-1992
			DE	69122471 D	07-11-1996
			DE	69122471 T	06-02-1997
			DK	485197 T	17-02-1997
			ES	2094796 T	01-02-1997
			GR	3021562 T	28-02-1997
			HK	1000733 A	24-04-1998
			JP	2724931 B	09-03-1998
			JP	4292609 A	16-10-1992
			US	5290892 A	01-03-1994
			US	5403901 A	04-04-1995
			US	5433746 A	18-07-1995
			US	5674960 A	07-10-1997
			US	5861031 A	19-01-1999
WO 9207885	A	14-05-1992	AT	146488 T	15-01-1997
			DE	69123756 D	30-01-1997
			DE	69123756 T	03-04-1997
			DK	555295 T	16-06-1997
			EP	0555295 A	18-08-1993
			ES	2094824 T	01-02-1997
			GR	3022397 T	30-04-1997
			HK	53297 A	02-05-1997
			JP	9020814 A	21-01-1997
			JP	2593993 B	26-03-1997
			JP	6502200 T	10-03-1994
			SG	43188 A	17-10-1997
WO 9211301	A	09-07-1992	US	5270415 A	14-12-1993
			CA	2098823 A	22-06-1992
			EP	0563299 A	06-10-1993
			EP	0751404 A	02-01-1997
			EP	0751405 A	02-01-1997
			EP	0751406 A	02-01-1997
			EP	0751407 A	02-01-1997
			JP	6508858 T	06-10-1994
			US	5391669 A	21-02-1995

PATENT COOPERATION TREATY

RECD 13 SEP 2000
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMJ02835WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04206	13/12/1999	11/12/1998
International Patent Classification (IPC) or national classification and IPC C08F246/00		
Applicant BIOCOMPATIBLES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/06/2000	08.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Knutzen-Mies, K Telephone No. +49 89 2399 8525

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04206

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-29 as originally filed

Claims, No.:

1-31 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-31
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-31
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-31
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

ad section V.:

None of the documents cited in the international search report, which have also been acknowledged at pages 1 and 2 of the present description, discloses or fairly suggests a crosslinked polymer obtainable by radical polymerisation of unsaturated monomers comprising a zwitterionic monomer, an aromatic group containing monomer and a crosslinking monomer as defined in claim 1 of the present application.

In particular, the combination of specific zwitterionic monomers with an aromatic group containing monomer to provide a polymer suitable for optical purposes such as eg intra ocular lenses, ie requiring a high refractive index, is not taught or suggested by the prior art.

The subject matter of claims 1 - 31 of the present application is therefore considered to fulfil the requirements of Article 33(2) - (4) PCT.

ad section VIII.:

The preferred embodiment of claim 5, ie R^9 being an ethylene or an oligo(ethylene-oxy)ethylene group, and the preferred range of crosslinking monomer in claim 10, ie 0.5 to 3 % by weight, have no descriptive counterpart (Article 84 PCT).

INTERNATIONAL SEARCH REPORT

Inter[redacted]Application No
PCT/GB 99/04206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08F246/00 G02B1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 485 197 A (NESTLE SA) 13 May 1992 (1992-05-13) cited in the application	
A	WO 92 07885 A (BIOCOMPATIBLES LTD.) 14 May 1992 (1992-05-14) cited in the application	
A	WO 92 11301 A (ALLERGAN INC.) 9 July 1992 (1992-07-09) cited in the application	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2000	24/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cauwenberg, C

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter[redacted] Application No
PCT/GB 99/04206

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